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Dr. Marilyn Kozak
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Dear Marilyn:

Thanks for sending me your paper, which I read with interest as usual. Since the data seem to be clear cut and the observations important, I cannot see why there should be major obstacles to publication in a journal like Cell. From an editorial point of view, I believe I would favor reducing the size of the paper by removing the several figures that simply document the nature of the constructs. (I have come to favor the idea that such information should be provided for the reviewers and supplied upon request to any who wish to see it.) I think you run the risk of offending some by your phrase "canting the theme" on p. 11. The description of our work with the 000 mutant will be inevitably (perhaps appropriately) obscure to most readers. I wonder whether some trimming of the manuscript would not allow you to include the other experiments in which you examine point mutations around an AUG: it seems to me that the two sets of data complement each other nicely.

If you encounter reactions of the sort you describe, I suspect that it is because the scanning model now seems to admit of so many more possibilities than it was originally conceived to do. What still seems central and testable is the notion that ribosomes work their way along mRNAs from 5' ends, perhaps ignoring some AUGs or restarting after termination codons, but not engaging mRNAs by direct assault upon internal positions. I think it helps to recognize that we are all still striving to understand what motivates initiation, without placing too much emphasis upon whether the rules that ultimately emerge can be accommodated within some modification of a hypothesis that has been enormously helpful in the past, but may have outgrown its utility as initially proposed.

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You may want to consider a few new retroviral items. Steve Hughes has mutated the stop codon that separates gag and src AUGs in src mRNA; as a result, a large portion of the src protein is now 3Kd larger than wild type. This, of course, suggests the gag AUG is still a perfectly good initiation site when spliced to form part of the leader in src mRNA. Perry Hackett (now at the U. Minn. Medical School) tells me that he has evidence for initiation at the first of the AUG's in the RSV leader (ribosome protection in the presence of anisomycin) and perhaps at the second AUG. Incidentally, we have raised antisera against a peptide from the 7 K domain but have yet to see the expected protein, though we are far from exhausting the means of detection.

I think the only way to deal with Paul Berg's data about reinitiation is to ask him for a "personal communication." He has described a couple of instances in a paper in MCB a couple of years ago, but (characteristically) has been slow to write up the rest.

With best regards,

Harold E. Varmus, M.D.
Professor

HEV/kyb